REMARKS

Claims 1-18, 22-25, 27-30, 32-44, and 46-61 are pending. Claims 2, 24, 25, 34, 36, 37, 47, 48, and 54-56 have been amended. Claims 27, 35, 57, and 58 have been canceled. Claims 1-18, 22-25, 28-30, 32-34, 36-44, 46-56, and 59-61 are therefore pending in the application.

Claims 2, 47, and 48 have been amended to correct typographical errors. Claims 24, 25, 34, 36, 37, and 54-56 have been amended to recite the diseases schizophrenia and depression. Support for these amendments can be found throughout the Specification, e.g., at page 2, lines 19-22. No new matter is introduced by these amendments.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 24, 25, 34, 35, 44, and 54-57 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner argued that the phrases "CNS disorder" and "disease mediated by the serotonin-related 5-HT_6 receptor" are indefinite. This rejection is moot in view of the amendments to claims 24, 25, 34, 44, and 54-56 and the cancellation of claims 35 and 57.

Rejection under 35 U.S.C. § 112, first paragraph

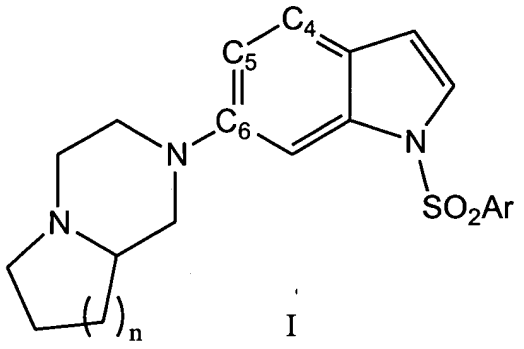
Claims 24, 25, 27, 44, and 54-58 were rejected under 35 U.S.C. § 112, first paragraph as not enabled. The Examiner argued that the claims are not enabled for treating "every CNS disorder" or "every disease mediated by the serotonin-related 5-HT_6 receptor." This rejection is moot in view of the amendments to claims 24, 25, 44, and 54-56 and the cancellation of claims 27, 57, and 58.

Rejection under 35 U.S.C. § 103(a)

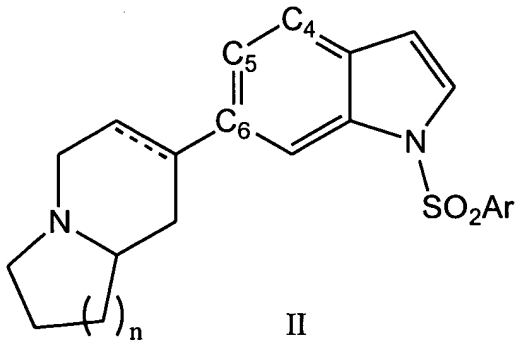
Claims 1-5, 11-13, 14, 18, 22-24, 27-30, 33-40, 44, 46-49, 54, 55, 57, 59, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isaac et al., *Bioorganic and Medicinal Chemistry Letters* **2000**, 1719 ("Isaac").

Isaac

Isaac discloses compounds having binding affinity for the 5-HT_6 receptor. The Isaac compounds (labelled as **4a-4g**, **13**, **16**, and **17** in Isaac) are 1-arylsulfonylindoles, all of which are substituted at C-6 (i.e., the 6-position) of the indole ring with a bicyclic, nitogenous heterocyclyl moiety. Compounds **4a-4g** are represented by formula (I), below, and compounds **13**, **16**, and **17** are represented by formula (II), below.



I



II

As discussed in detail in the previous response, Isaac provides no suggestion or motivation to synthesize and investigate compounds having the hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl radical or any heterocyclyl radical at C-4 or C-5 of the indole ring. Isaac focused on other aspects of the molecule, e.g., the nature of the aryl sulfonyl moiety (i.e., "Ar") and the nitrogen content and ring size (i.e., "n") of the exclusively bicyclic heterocyclyl moiety.

The Rejection

In the Action, the Office does not dispute the absence in Isaac of any suggestion or motivation to vary the point of attachment of the heterocyclyl moiety, much less any suggestion or motivation to attach the heterocyclyl moiety to the C-4 or C-5 position of the indole ring. However, the Office argues that compounds with a heterocyclyl moiety attached at the C-4 or C-5 position of the indole ring are "*per se* ring obvious position isomers" of the compounds in Isaac. The Office argues that no secondary teaching is required because varying the point of attachment of the heterocyclyl moiety to the indole ring would be merely "routine" for a "medicinal chemist." According to the Action:

> Applicants argue that there is no teaching within the reference to move the point of attachment, ... This is not persuasive. Concerning the first argument, these are *per se* obvious ring position isomers and no secondary teaching is required. It would be routine for the medicinal chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds (Action, part 7, page 15, emphasis added).

Applicants respectfully disagree.

There are no *per se* rules of obviousness.

The obviousness inquiry of 35 U.S.C. § 103 requires a comparative analysis of the claimed "subject matter as a whole" with the prior art "to which said subject matter pertains" *In re Ochiai* 37 USPQ2d 1127, 1131 (Fed. Cir. 1995). "The inquiry is thus highly fact-specific by

design" (*Id.*). The Court in *In re Ochiai* unequivocally stated that there is no judicial precedent for *per se* rules of obviousness and that use of such rules is "legally incorrect":

> No *per se* rules of obviousness have been established by precedent, and reliance on any such rules that eliminate need for fact-specific analysis of claims and prior art is legally incorrect and must cease, since use of *per se* rules in obviousness determination is inconsistent with 35 U.S.C. 103, ... The use of *per se* rules, while undoubtedly less laborious than a searching comparison of the claimed invention-including all its limitations-with the teachings of the prior art, flouts section 103 and the fundamental case law applying it. *Per se* rules that eliminate the need for fact-specific analysis of claims and prior art may be administratively convenient for PTO examiners and the Board. Indeed, they have been sanctioned by the Board as well. But reliance on *per se* rules of obviousness is legally incorrect and must cease (*Id.* at 1127, 1133).

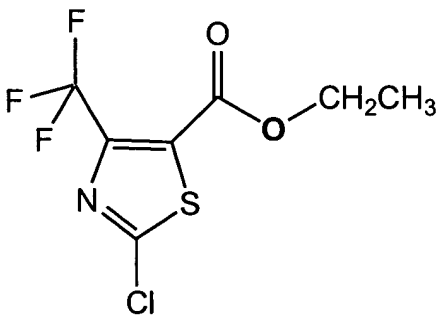
Applicants submit that there is simply no legal basis for concluding that the claimed compounds are "*per se* obvious ring position isomers."

Prior art must provide reason or motivation to make claimed compound.

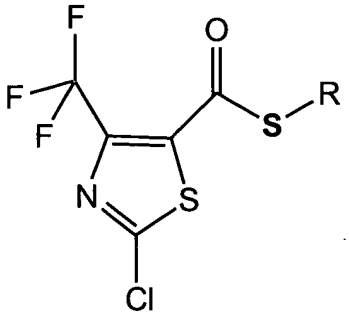
The Federal Circuit (*in banc*) in *In re Dillon* reaffirmed that a *prima facie* case of obviousness of a chemical composition can be established if there is "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions" *In re Dillon* 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*In Banc*). It is well established that the reason or motivation to make the claimed compound must be found in the prior art to which the claimed subject matter pertains. In other words, the prior art must suggest the modifications needed to arrive at the claimed compound from a known reference compound. The mere fact that a particular modification can be made (i.e., it is chemically feasible or apparent to a chemist) is insufficient to show a reason or motivation to make the claimed compound unless it is coupled with a prior art teaching or suggestion that such a modification would be desirable:

> Board's finding of prima facie case of obviousness predicated on obviousness of compounds' structure to a chemist is not necessarily conclusive as to obviousness of subject matter as a whole *In re Stemniski*, 444 F.2d. 581, 170 USPQ 343 (CCPA 1971).
>
> The mere chemical possibility that one of those prior art acids could be modified such that its use would lead to the particular cepham recited in claim 6 does not make the process recited in claim 6 obvious 'unless the prior art suggested the desirability of [such a] modification' *In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) (quoting *In re Gordon* 733 F.2d 900, 902, 221USPQ 1125, 1127 (Fed. Cir. 1984)).

As explained in the seminal case of *In re Papesch*, the problem of chemical obviousness "is not really a problem of chemistry...It is a problem of *patent law*" *In re Papesch*, 315 F.2d. 381, 137 USPQ 43, 47 (CCPA 1963) (emphasis in original). The Court of Appeals for the Federal Circuit in *In re Grabiak* considered the obviousness of a claimed compound *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). In *Grabiak*, appellants' compounds (exemplified below on the right hand side) are herbicidal safener compounds that include a thioester moiety (i.e., -C(O)**S**R) attached to a heterocyclic ring. A prior art reference (Howe) disclosed an herbicidal safener compound (shown below on the left hand side) that contained a "normal ester" (i.e., -C(O)**O**R) attached to an otherwise identical heterocyclic ring. In short, appellants' compounds and the prior art compound had the same asserted utility, but differed only in the identity of one constituent atom (O *versus* S).



Reference



Appellants'

The Examiner rejected claims to Grabiak's compounds under 35 U.S.C. § 103(a) over Howe in view of two other references, Bollinger and Conant. Bollinger disclosed that activity of certain heterocyclic-based safener compounds was preserved when sulfur and oxygen were exchanged within the heterocyclic ring. The Conant reference, an organic chemistry textbook, disclosed the equivalence of properties between simple oxygen compounds and their sulfur analogs. None of the cited references, however, taught or suggested the modification of replacing the ester oxygen of the Howe compounds with a sulfur atom. Based on these findings, the Court concluded:

> The PTO cited no pertinent reference showing or suggesting to one of ordinary skill in the art the change of a thioester for an ester group. In the absence of such reference, there is inadequate support for the PTO's position that this modification would be prima facie obvious (*Id.* at 872, emphasis added).

The present rejection

The Office has erred both by arguing that there can exist "per se obvious ring position isomers" and by failing to cite any legally cognizable reason or motivation to modify the compounds of Isaac to arrive at the presently claimed compounds. As the Court of Appeals for the Federal Circuit has made clear, there are no *per se* rules of obviousness (*In re Ochiai, supra*). The Court has also made clear that, in the case of chemical compounds, the art must provide a reason or motivation to modify the prior art compound (*In re Dillon*, supra).

The reason or motivation is clearly not provided by Isaac. What guidance is provided by Isaac is completely unrelated to varying the point of attachment of the heterocyclyl moiety. Isaac indicates only that the lipophilicity of the sulfonyl aryl group and ring size/nitrogen content of the bicyclic heterocyclyl moiety were important to activity. Moreover, Isaac made no effort to vary the position of the substitution on the indole ring. Instead, Isaac elected to investigate compounds having other heterocyclyl moieties at the 6-position, i.e., 6-(6,5-bicyclopiperidine) analogues, rather than explore positional isomer analogues:

> Of the monocyclic and bicyclic aromatic sulfonyl groups studied, the lipophilic bicyclic substituent such as the 1-naphthyl group were beneficial to 5-HT6 receptor affinity. The rapid optimization of the aryl sulfonyl groups (1-naphthyl group favored) along with the realization that the 6,5-bicyclopiperazine-systems were generally more potent than the corresponding 6,6-bicyclopiperazine homologue, prompted us to examine the 6,5-bicyclopiperidine analogues (**16** and **17**) (Isaac at page 1720).

Given Isaac's teaching that increasing lipophilicity of the sulfonyl aryl group and changing the size and nitrogen content of the bicyclic heterocyclic moiety are important for optimizing activity, why then would the art modify, for example, a 0.2 nM compound (i.e., compound **4a**; Formula (I), Ar = 1-naphthyl and n = 1) in a way that is completely unrelated to either increasing the lipophilicity of the arylsulfonyl group or changing the ring size or nitrogen content of the heterocyclyl moiety? Put simply, why would the art vary the point of attachment of the heterocyclyl moiety in these generally very potent compounds when such a modification is neither taught nor suggested by Isaac?

Clearly, Isaac provides absolutely no reason or motivation to modify the attachment points, much less a motivation to create a C-4 or C-5 substituted indole. Having failed to find a reason or motivation in the art, the Office provided the sweeping conclusory statement that "[i]t would be routine for the medicinal chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds." Such a sweeping, unsubstantiated generalization clearly fail to meet the legal standards for showing reason or

motivation to modify as established, e.g., in *Ochiai*, *Stemniski* or *Grabiak*, discussed above. As such, these assertions do not perfect the Office's prima facie case. If the desire to improve activity of a pharmaceutical compound or obtain patent protection were a legally cognizable reason or motivation to modify a prior art compound, it would be a basis for finding prima facie obvious any chemical compound that bore any structural similarity to a prior art pharmaceutical compound. This is clearly not the standard set by the relevant case law.

Finally, the CCPA stated in *Papesch* "[f]rom the standpoint of patent law, a compound and all of its properties are inseparable;... *In re Papesch* 137 USPQ 43, 47 (CCPA 1963). Applicants point out that the four substitutable carbons (i.e., C-4, C-5, C-6, C-7) of the indole six-membered ring are nonequivalent (e.g., C-6 is in closer proximity to the indole nitrogen than C-4 or C-5) and are sp^2 hybridized (i.e., have a trigonal planar geometry). One of skill in the art would recognize that moving the heterocyclyl radical from C-6 to C-4 or C-5 would result in compounds clearly having significantly different shapes, dipole moments, etc. Terms such as "positional isomer" infer that one or more similarities (e.g., in structure and/or properties) exist among a particular family of positional isomers. Whether such similarities extend to the properties of a given set of positional isomers must be determined on a case by case basis. Given the structural attributes of the indole skeleton discussed above and given that drug-receptor binding is highly sensitive to substrate molecular geometry, one of skill in the art would <u>not</u> necesssarily have the expectation that the C-4/C-5 isomers would have the same properties as the C-6 positional isomer for the reasons set forth above. Applicants again submit that this conclusion is bourne out in the water solubility data included with the previously filed response. Again, no evidence is provided in the Action to establish why a C-6 substituted indole compound would necessarily be expected to function similarly to a C-4 or C-5 substituted indolyl compound.

In view of the foregoing, Applicants submit that the Office has failed to meet its burden of establishing a prima facie case obviousness on the grounds set forth above. Since the claimed compounds are nonobvious over Isaac, then Applicants' claims directed to pharmaceutical compositions and methods of using the claimed compounds also are not rendered obvious by

Isaac. As such, Applicants repectfully request withdrawal of the rejection of claims 1-5, 11-13, 14, 18, 22-24, 27-30, 33-40, 44, 46-49, 54, 55, 57, 59, and 60.

Enclosed is a $950.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No.: 13425-052001.

Respectfully submitted,

Date: July 13, 2004

John T. Kendall
Reg. No. 50,680
FOR Anita L. Meiklejohn, Ph.D.
Reg. No. 35,283

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906